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EXAMINER	
HILL, KEVIN KAI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/797,289	SCOTT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-80 and 89-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-80 and 89-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

1. In the reply filed January 8, 2007, Applicant has amended Claims 77-80, 89-100, 109-116 and 125-136, and cancelled Claims 81-88 and 137-140.

Claims 77-80 and 89-136 are under consideration.

Claim Objections

2. **Claims 77-80 are newly objected to because of the following informalities**: the comma after the term 'gene-targeted' separates the adjective from its subject. Furthermore, the terms 'said rodent' and 'said mammal' are broader in scope than the gene-targeted mouse, and thus do not precisely agree with the subject composition of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 77-80 and 89-136 stand rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use

the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claimed product invention(s) is drawn to gene-targeted rodents comprising three distinct genetic elements:
A) heterozygous or homozygous for a gene-targeted knock-in mutation of the rodent presenilin-1 (PS-1) gene, wherein the mutation is a PS-1 mutation discovered in human Familial Alzheimer's disease,
B) heterozygous or homozygous for an amyloid precursor protein (APP) transgene having a human FAD Swedish mutation, and
C) a knock-in mutation of the endogenous rodent APP gene, wherein the mutation comprises a "humanized" A-beta nucleotide sequence.

The claimed method inventions are directed to methods using the claimed rodents for:
i) screening chemical compounds for the ability to decrease *in vivo* levels of A-beta40 or A-beta42 peptide, obtaining a tissue sample from the claimed rodent, e.g., brain tissue, non-brain tissue, and body fluids, and measuring the relative amount of A-beta40 or A-beta42 peptide in the tissue sample (Claims 93-108), and
ii) identifying chemical compounds for treating Alzheimer's disease, wherein the compound has the ability to decrease *in vivo* levels of A-beta40 or A-beta42 peptide, the method comprising the steps of obtaining a tissue sample from the claimed rodent, e.g., brain tissue, non-brain tissue, and body fluids, and measuring the relative amount of A-beta40 or A-beta42 peptide in the tissue sample, wherein a decrease in the amount of A-beta peptide in the assayed tissue sample is indicative of a compound that can be used to treat Alzheimer's disease (Claims 109-124).

The claims are also broad for using narrative and descriptive language as applied to the structural nucleic acid sequence of "a human FAD Swedish mutation", thus encompassing an enormous genus of FAD mutations in humans having an undefined degree of Swedish ethnicity which is entirely irrelevant to the structural nature of the FAD mutation, and thus places essentially no restrictions as to the genetic sequence of the inventive FAD mutation extant in the gene-targeted mouse. When the claims are analyzed in light of the specification, the inventive concept is the introduction of a transgene into the murine genome that encodes the APP double mutation K595N and M596L found in human patients of Swedish descent (page 6, lines 2-14), and which is genetically propagated in the mouse line Tg2576 (Hsiao et al, 1996), and thus indicated herein as Tg2576 or APP695Swe.

The claims are broad for encompassing an enormous genus of "humanized" A-beta nucleotide sequences. Again, narrative and descriptive language is applied to a structural element, that is the nucleotide sequence encoding an A-beta polypeptide. When the claims are

analyzed in light of the specification, the inventive concept is the gene-targeted knock-in of the murine APP locus, wherein the knocked-in mutation encodes the APP695Swe mutation, K595N and M596L described above, along with an additional modified amino acid sequence (Reaume et al, 1996, page 23382, Figure 1), and thus indicated herein as APP^{NLh}.

The claimed methods are broad for encompassing a vast genus of structurally diverse chemical compositions. Applicant contemplates the chemical compounds to be "any identifiable chemical or molecule", e.g. a peptide, a protein, a sugar or a nucleotide (page 19, lines 20-24).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

While the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce any transgenic animal that exhibits a desired phenotype, regardless of whether a gene targeted modification technique, rather than the traditional introduction of a desired exogenous protein-encoded construct, is used to introduce the recombinant nucleic acid into embryonic cells.

Applicant contemplates that by targeting any DNA vector construct encoding any 264 codon-mutant PS-1 gene product ($PS\text{-}1^{P264L}$, for example) or a human APP polypeptide comprising the Swedish mutation (APP^{NLh}) via homologous recombination into an endogenous genomic site containing the endogenous gene of any rodent cell, including pluripotent, embryo-derived stem (ES) cells, can produce a knock-in rodent comprising germ-line chimera as the result of fusion between the genetically modified ES cell and the rodent embryos (page 10).

At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells. Palmiter et al (PNAS 88: 478-482, 1991) teach that directed expression of any gene to any specific cell type of an animal by using established transgenic methodology is theoretically possible by combining the regulatory regions(s) of a gene that is expressed in a cell-specific manner with any mRNA-encoding structural gene. Palmiter et al, note, however, that not all gene constructs work well; the two most common problems are inappropriate expression patterns and failure to achieve adequate expression levels (page 478, left column, first paragraph). Wall (Theriogenology 45: 57-68, 1996) discloses the unpredictability of transgene behavior due to factors such as unidentified control elements (during the fusion between ES cell and embryos) and may result in variable expression. Whitelaw et al (Transgenic Research 1(1): 3-13, 1991, page 10, columns 1-2, joining paragraph) indicates that exogenous DNA, constructs, intron-less constructs or constructs containing the introns, do affect variation in gene expression. Palmiter (Ann Rev. Genetics 20: 465-498, 1986) indicates that variable inappropriate expressions do often occur in transgenic founder animal and/or offspring (pages 482 and 483).

Although Applicant possesses mice comprising any combination of two of the three inventive elements ($PS\text{-}1^{P264L/P264L}$, $APP^{NLh/NLh}$ and Tg2576, see below) wherein said double transgenic mice demonstrate a phenotype, the disclosed double transgenic condition cannot be reasonably extrapolated to the enormous genus of genetically engineered mice that contain all

three inventive genetic elements and is heterozygous or homozygous for any one or all three inventive genetic elements (the enormous genus of human PS-1 mutations, $APP^{NLh/NLh}$ and Tg2576). Thus, it is reasonably unpredictable for one skilled in the art to produce any transgenic animal that contains all three inventive genetic elements to exhibit a desired phenotype, based on the phenotype of a small subset of double transgenic animals.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The claims are readable on an enormous genus of gene-targeted rodents heterozygous or homozygous for genes encoding human Familial Alzheimer's disease mutations. The specification contemplated that the claimed gene-targeted rodent for a presenilin-1 (PS-1) mutation, an amyloid precursor protein (APP) transgene having a human FAD Swedish mutation, and a knock-in mutation of a "humanized" Aβ nucleotide sequence of the rodent APP gene either exhibits the pathology and symptoms of Alzheimer's disease, or can be used in a screening assay to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemicals compounds for their ability to inhibit the formation of Aβ42 peptides in the brain tissues, other tissues, and body fluids (page 4, lines 18-20; page 5, lines 20-22; page 6, lines 1-2; page 7, lines 11-13; page 9, lines 13-25).

The specification provides working examples showing the making by ES technology and cross-breeding of a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and the APP695Swe mutation, K595N and M596L, said mouse comprising in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type mouse.

However, the specification does not provide sufficient guidance and/or evidence to demonstrate possession of genetically-engineered mice containing all three inventive genetic elements ($PS\text{-}1^{nP264L/nP264L}$, $APP^{NLh/NLh}$ and Tg2576) that exhibit an increase of endogenous Aβ42 peptides relative to that of wild-type mice and manifest the contemplated properties, e.g., Alzheimer's disease phenotypes. All examples in the instant application disclose mice that are either heterozygous or homozygous for one or two of the genetic elements, but never containing at least one of each of the three inventive genetic elements. As there is no demonstration of possession of genetically-engineered mice containing all three inventive genetic elements, it follows that there are no disclosures for the creation of triple mutant mice, or generational offspring thereof, wherein the generational offspring also comprise at least one of each of the three genetic elements (page 13, lines 3-12), and what, if any, phenotype these triple transgenic mice manifest. In the absence of the demonstration of a genetically-engineered mouse comprising all three inventive genetic elements, and in light of the nature of the mutations and their consequent effects on the development of the brain and nervous system tissues, one of ordinary skill in the art can reasonably question the *de facto* viability of the claimed genetically-engineered mouse, wherein the mouse comprises at least one of each of the three inventive genetic elements and is heterozygous or homozygous for any one or all three inventive genetic elements ($PS\text{-}1^{nP264L/nP264L}$, $APP^{NLh/NLh}$ and Tg2576). Given that there is no example of a mouse comprising at least one of each of the three inventive genetic elements, it also follows that there is no disclosure or working example guiding one of ordinary skill in the art how to screen for

compounds for the ability to decrease *in vivo* levels of Aβ peptide or for identifying a compound for treating Alzheimer's disease, wherein both methods comprise the method step of administering a compound to the inventive mouse comprising at least one of each of the three inventive genetic elements, that is PS-$1^{nP264L/nP264L}$, $APP^{NLh/NLh}$ and Tg2576.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The claims encompass a genus of transgenic mice comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic rodent other than mice. Taken together, the current status of transgenic art is such that generating a genus of transgenic mice with a requisite phenotype, e.g., FAD, is neither routine nor predictable, unless proven by a working example, let alone a claim that embraces any transgenic rodent other than a mouse as claimed. Furthermore, the specification provides limited guidance on page 5 with regard to phenotypic expression of the P264L mutation. The specification indicates that the P264L mutation in humans caused an increased amount of amyloid Aβ42 protein, and is involved in clinical manifestation of Alzheimer's disease. However, neither the specification nor its incorporated references provides any teaching on any biological effect on the amount of murine amyloid Aβ42 protein expression or clinical manifestation of Alzheimer's disease in the mouse of the invention. Note that incorporation and expression of a human P264L mutant PS1 encoded construct as a foreign genetic construct into any murine cell which is subsequently used for fusion with a murine embryo so a to produce a founder genetically modified mouse does not necessarily mean a reasonable predictability of a phenotypic expression in the founder transgenic mouse for any detectable phenotype and/or phenotypic offspring thereof. Furthermore, there is no evidence either from the specification or from the prior art that a correct introduction via homologous recombination of a human mutant P264L PS-1 gene into a mouse having a murine genome encoding distinct murine proteins, and having a distinct physiology and chemical pathways would generate any phenotype of FAD.

With respect to the claimed methods, the specification fails to provide sufficient guidance and/or assay systems to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemical compounds for their ability to inhibit the formation, presence, and deposition of excessive amounts of Aβ40 or Aβ42 for the treatment of Alzheimer's disease in any tissues obtained from the claimed genetically-engineered mouse, wherein the mouse comprises at least one of each of the three inventive genetic elements and is heterozygous or homozygous for any one or all three inventive genetic elements (PS-$1^{nP264L/nP264L}$, $APP^{NLh/NLh}$ and Tg2576), as no specific teachings regarding the existence, viability or any phenotype whatsoever, of said inventive mouse are disclosed. As discussed above, it is reasonably unpredictable for one skilled in the art to produce any transgenic animal that contains all three inventive genetic elements (the enormous genus of human PS-1 mutations, $APP^{NLh/NLh}$ and Tg2576), heterozygously, homozygously or combinations thereof, and will exhibit a desired phenotype, based on the phenotype of a small subset of double transgenic animals.

The data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Thus, based upon the evidence

in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph.

Applicant's Arguments

Applicant argues that:

a) the enablement requirement is fulfilled if any mode of making and using the invention is described, e.g. methods of making mice having an amyloid precursor protein (APP) gene having a human FAD Swedish mutation and humanized Aβ nucleotide sequence were known in the art, and

b) the specification provides ample guidance regarding the methods of making and using the claimed mice.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the Examiner acknowledges the disclosure in the instant specification regarding creation of gene-targeted mice comprising a single transgene, e.g. PS-$1^{nP264L/nP264L}$, $APP^{NLh/NLh}$ or Tg2576, and the mating of a single, gene-targeted mouse line to another single, gene-targeted mouse line, e.g. PS-$1^{nP264L/nP264L}$ x Tg2576, wherein the progeny of such a cross yields a phenotype (see, for example, pg 38, Table 4). However, the instantly claimed subject matter is a triple gene-targeted mouse. Applicant has provided no evidence regarding the phenotype of the claimed mouse so as to inform the artisan what phenotypes may be assayed when performing the claimed methods. The art recognizes significant unpredictability in the phenotype of transgenic animals, and thus one of ordinary skill cannot reasonably extrapolate the phenotype(s) observed in the double gene-targeted mice to the recited and undisclosed triple gene-targeted mice.

With respect to b) as pointed out be the Examiner, the specification discloses single and double gene-targeted mice, and their respective phenotypes. Applicant has failed to direct the Examiner to specific examples in the disclosure that describe the phenotype(s) of the triple gene-targeted mice. The substantive issue is the absence of sufficient disclosure under 35 U.S.C. 112, first paragraph "how to make" and "how to use" requirements. Applicant has provided no evidence regarding the phenotype(s) of the triple gene-targeted mouse, and thus has failed to

demonstrate a constructive or actual reduction to practice regarding the "making" of the claimed triple gene-targeted mouse. It necessarily follows that Applicant has provided no evidence regarding a constructive or actual reduction to practice the claimed methods on the claimed triple transgenic rodents.

Proof of a constructive reduction to practice requires sufficient disclosure under the "how to use" and "how to make" requirements of **35 U.S.C. 112**, first paragraph. *Kawai v. Metlesics*, 480 F.2d 880, 886, 178 USPQ 158, 163 (CCPA 1973) (A constructive reduction to practice is not proven unless the specification discloses a practical utility where one would not be obvious. Prior art which disclosed an anticonvulsant compound which differed from the claimed compound only in the absence of a –CH.

The same evidence sufficient for a constructive reduction to practice may be insufficient to establish an actual reduction to practice, which requires a showing of the invention in a physical or tangible form that shows every element of the count. *Wetmore v. Quick*, 536 F.2d 937, 942, 190 USPQ 223, 227 (CCPA 1976). For an actual reduction to practice, the invention must have been sufficiently tested to demonstrate that it will work for its intended purpose, but it need not be in a commercially satisfactory stage of development. >See, e.g., *Scott v. Finney*, 34 F.3d 1058, 1062, 32 USPQ2d 1115, 1118-19 (Fed. Cir. 1994)(citing numerous cases wherein the character of the testing necessary to support an actual reduction to practice varied with the complexity of the invention and the problem it solved).< See MPEP 2138.05

Id. at 533, 226 USPQ at 621. *See also In re Borst*, 345 F.2d 851, 855, **145 USPQ 554, 557** (CCPA 1962) ("the disclosure must be such as will give possession of the invention to the person of ordinary skill. Even the act of publication or the fiction of constructive reduction to practice will not suffice if the disclosure does not meet this standard.").

Although Applicant foresees a triple transgenic mouse, the specification fails to disclose the phenotype(s) of the desired mutated mouse. The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, must supply the novel aspects of an invention in order to constitute adequate enablement". (See

Genentech Inc v. Novo NordiskA/S 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Conclusion

4. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER